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EXAMINER
CHAKRABARTI, ARUN K

ART UNIT	PAPER NUMBER
1634	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/768,936	Patil, N.	
	Examiner	Art Unit	
	Arun Chakrabarti	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

Specification

1. Claims 1, 13-16, 18, and 35 have been amended.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-6 and 12-14 are rejected under 35 U.S.C. 103 (a) over Sicilliano et al. (U.S. Patent 5,538,869) (July 23, 1996) in view of Cronin et al. (U.S. Patent 6,309,823 B1) (October 30, 2001).

Sicilliano et al teach a method of analyzing a subset of nucleic acids within a nucleic acid population (Abstract and Examples 4-7):

a) providing a population of nucleic acid fragments at least some of which have sequences that are repeated more than once in a genome (Column 7, line 44 to column 8, line 26 and Example 4 and Figure 20 and Prophetic Example 12);

b) incubating single stranded forms of the population of nucleic acid fragments under annealing conditions, whereby single stranded forms of nucleic acid fragments having repeat sequences preferentially hybridize to each other relative to nucleic acid fragments lacking repeat sequences (Claims 1-16 and Examples 1-6 and Figure 20 and Prophetic Example 12) ;

c) separating single stranded forms of the population of nucleic acid fragments from annealed double stranded forms, the single stranded forms being enriched for nucleic acid fragments lacking repeat sequence (Column 14, line 37 to column 15, line 14);

d) inherently hybridizing the separate single stranded forms of the population of nucleic acid fragments to a nucleic acid probe array and inherently teaches that annealed double-stranded forms being enriched for nucleic acid fragments containing repeat sequences (metaphase spreads are considered as nucleic acid probe array as taught in Column 14, line 37 to column 15, line 14) ;

e) determining hybridization of the probes to the single stranded forms of the population of nucleic acid fragments, thereby analyzing the fragments (Figures 3-19 and Examples 8-10).

Sicilliano et al teach a method wherein the population of nucleic acid fragments span the chromosome of the human genomic fragments (Examples 4-8).

Sicilliano et al teach a method further comprising denaturing the population of nucleic acid fragments before the incubation step (Figure 20 and Prophetic Example 12).

Sicilliano et al teach a method wherein the determining indicates the presence of at least one variation in a fragment hybridized to the array relative to the reference sequence (Example 8 and Column 25, line 33 to column 28, line 25).

Sicilliano et al teach a method wherein the population of nucleic acid are from a chromosome from a first individual, and the reference sequence is that of a corresponding chromosome from a second individual (Column 25, line 33 to column 28, line 25).

Sicilliano et al do not teach an array, which comprises a set of probes complementary to a known reference sequence, the reference sequence being the same or variant of the sequence of a nucleic acid from which the population of nucleic acid fragments was obtained.

Cronin et al. teach an array, which comprises a set of probes complementary to a known reference sequence, the reference sequence being the same or variant of the sequence of a nucleic acid from which the population of nucleic acid fragments was obtained (Abstract and Figures 1-9, and Example and Column 14, line 46 to Column 15, line 56).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine an array, which comprises a set of probes complementary to a known reference sequence, the reference sequence being the same or variant of the sequence of a nucleic acid from which the population of nucleic acid fragments was obtained of Cronin et al. into the identification and banding of human chromosome of Sicilliano et al., since Cronin et al. state "An array of probes is most useful for analyzing the reference sequence from which the probes were designed and variants of that sequence exhibiting substantial sequence similarity with the reference sequence (e.g., several single base mutations spaced over the reference sequence) (Column 14, lines 46-50." Cronin et al provides further motivation as Cronin et al. state, "A particular advantage of the present sequencing strategy over conventional sequencing methods is the capacity simultaneously to detect and quantify proportions of multiple target sequences (Column 15, lines 30-33)". An ordinary practitioner would have been motivated to substitute and combine an array, which comprises a set of probes complementary to a known reference sequence, the reference sequence being the same or variant of the sequence of a nucleic acid from which the population of nucleic acid fragments was obtained of Cronin et al. into the identification and banding of human chromosome of Sicilliano et al, in order to achieve the express advantages, as noted by Cronin et al., of an array of probes, which is most useful for analyzing the reference sequence from which the probes were designed and variants of that sequence exhibiting substantial sequence similarity with the reference sequence (e.g., several single base mutations spaced over the reference sequence) and which also

provides a particular advantage over conventional sequencing methods with its capacity of detecting and quantifying proportions of multiple target sequences simultaneously.

4. Claims 15-18 are rejected under 35 U.S.C. 103(a) over Austin et al. (U.S. Patent 6,132,965) (October 17, 2000) in view of Cronin et al. (U.S. Patent 6,309,823 B1) (October 30, 2001).

Austin et al teach a method for analyzing a subset of nucleic acids within a nucleic acid population (Abstract and Claims 1-2), comprising:

a) providing driver and tester population of nucleic acids (Column 22, lines 40-50 and Column 7, line 14 to column 8, line 34);

b) hybridizing the driver and tester populations with each other (Column 22, lines 51-55 and Column 7, line 14 to column 8, line 34);

c) separating nucleic acids from the tester populations that hybridize to the driver population from tester nucleic acids that do not hybridize (Column 22, lines 56-64 and Column 7, line 14 to column 8, line 34);

d) hybridizing either the tester nucleic acids that do hybridize to the driver population, or the tester nucleic acids that do not hybridize to the driver population to a nucleic acid probe array (Column 22, line 64 to column 23, line 4 and Column 7, line 14 to column 8, line 34);

e) determining hybridization of the probes to the tester nucleic acids thereby analyzing the tester nucleic acids (Column 23, lines 18-21 and Column 7, line 14 to column 8, line 34).

Austin et al teach a method wherein the driver population of nucleic acids each bear a tag by which the driver population of nucleic acids can be immobilized to a binding moiety with affinity for the tag (Column 22, lines 51-61 and Column 7, line 14 to column 8, line 34).

Austin et al teach a method wherein the tag is biotin, and the binding moiety is avidin (Column 22, lines 51-61 and Column 7, line 14 to column 8, line 34).

Austin et al teach a method wherein the separating step is performed by immobilizing the driver population of nucleic acids and tester population of nucleic acids hybridized to the driver population via the tags of the driver population (Column 22, lines 56-61 and Column 7, line 14 to column 8, line 34).

Austin et al teach a method wherein the driver population of nucleic acids are a population of DNA fragments, and the tester nucleic acids are a population of mRNA or nucleic acids derived therefrom, and the method further comprises denaturing tester nucleic acids from the driver population of nucleic acids, the resulting tester nucleic acids showing reduced variance in copy number between different fragments than in the population of mRNA or nucleic acids derived therefrom; and wherein the resulting tester nucleic acids are hybridized to the array (Column 22, line 64 to column 23, line 4 and Column 23, line 24 to column 24, line 50 and Column 7, line 14 to column 8, line 34).

Austin et al teach a method wherein the driver population of nucleic acids are a population of DNA from a first source, and the tester population of nucleic acids are DNA from a second source and the method further comprises denaturing tester nucleic acids from the driver

population of nucleic acids, the resulting tester nucleic acids being enriched for tester nucleic acids having common sequences with the driver population of nucleic acids relative to the population of tester nucleic acids, and wherein the resulting tester nucleic acids are hybridized to the array (Column 22, line 64 to column 23, line 4 and Column 7, line 14 to column 8, line 34)..

Austin et al teach a method wherein the at least one region is a PCR amplification product (Column 23, lines 44-52).

Austin et al teach a method wherein the driver population of nucleic acids are from a plurality of noncontiguous regions of the genome (Figure 5).

Austin et al teach a method wherein the driver population of nucleic acids are format least 10 noncontiguous regions of the genome (Figure 5).

Austin et al teach a method wherein the method is repeated for at least ten further population of tester nucleic acids from at least ten further source of the same human species (Column 35, lines 34-37).

Austin et al teach a method wherein the driver population of nucleic acids are DNA from a first source, and the tester population of nucleic acids are DNA from a second source and the tester nucleic acids that do not hybridize to the driver fragments are hybridized to the array, these tester nucleic acids being enriched for nucleic acids having sequences not common with sequences of the nucleic acids in the driver population (Column 22, line 64 to column 23, line 4 and Column 23, line 24 to column 24, line 50 and Column 7, line 14 to column 8, line 34).

Austin et al teach a method wherein the first and second sources are from the same or different species (Column 8, lines 15-34).

Austin et al teach a method wherein the population of driver nucleic acids are mRNA or nucleic acids derived therefrom a first source, and the population of tester nucleic acids are mRNA or nucleic acids derived therefrom from a second sources, the tester nucleic acids that do not hybridize with the driver nucleic acids are hybridized to the array, these tester nucleic acids being enriched for sequences present in the second source and absent in the first source (Column 22, line 64 to column 23, line 4 and Column 23, line 24 to column 24, line 50 and Column 7, line 14 to column 8, line 34).

Austin et al do not teach an array, which comprises a set of probes complementary to a known reference sequence, the reference sequence being the same or variant of the sequence of a nucleic acid from which the population of nucleic acid fragments was obtained.

Cronin et al. teach an array, which comprises a set of probes complementary to a known reference sequence, the reference sequence being the same or variant of the sequence of a nucleic acid from which the population of nucleic acid fragments was obtained (Abstract and Figures 1-9, and Example and Column 14, line 46 to Column 15, line 56).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine an array, which comprises a set of probes complementary to a known reference sequence, the reference sequence being the same or variant of the sequence of a nucleic acid from which the population of nucleic acid fragments was

obtained of Cronin et al. into the method for analyzing a subset of nucleic acids within a nucleic acid population of Austin et al., since Cronin et al. state "An array of probes is most useful for analyzing the reference sequence from which the probes were designed and variants of that sequence exhibiting substantial sequence similarity with the reference sequence (e.g., several single base mutations spaced over the reference sequence) (Column 14, lines 46-50." Cronin et al provides further motivation as Cronin et al. state, "A particular advantage of the present sequencing strategy over conventional sequencing methods is the capacity simultaneously to detect and quantify proportions of multiple target sequences (Column 15, lines 30-33)". An ordinary practitioner would have been motivated to substitute and combine an array, which comprises a set of probes complementary to a known reference sequence, the reference sequence being the same or variant of the sequence of a nucleic acid from which the population of nucleic acid fragments was obtained of Cronin et al. into the method for analyzing a subset of nucleic acids within a nucleic acid population of Austin et al, in order to achieve the express advantages, as noted by Cronin et al., of an array of probes, which is most useful for analyzing the reference sequence from which the probes were designed and variants of that sequence exhibiting substantial sequence similarity with the reference sequence (e.g., several single base mutations spaced over the reference sequence) and which also provides a particular advantage over conventional sequencing methods with its capacity of detecting and quantifying proportions of multiple target sequences simultaneously.

5. Claims 1-14 are rejected under 35 U.S.C. 103 (a) over Sicilliano et al. (U.S. Patent 5,538,869) (July 23, 1996) in view of Cronin et al. (U.S. Patent 6,309,823 B1) (October 30, 2001) further in view of Arnold et al. (U.S. Patent 5,714,354) (February 3, 1998).

Sicilliano et al in view of Cronin et al. teach the method of claims 1-6 and 12-14 as described above.

Sicilliano et al in view of Cronin et al. do not teach the separation of nucleic acid fragments by successively performing hydroxyapatite chromatography and HPLC.

Arnold et al teach the separation of nucleic acid fragments by successively performing hydroxyapatite chromatography and HPLC (Figure 7, Example 1, Column 8, lines 43-46 and Example 2, Column 8, lines 55-59).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the separation of nucleic acid fragments by successively performing hydroxyapatite chromatography and HPLC of Arnold et al. into the identification and banding of human chromosome of Sicilliano et al. in view of Cronin et al., since Arnold et al. state "The final purification step utilizing hydroxyapatite yields a highly purified product as indicated by the HPLC chromatogram and corresponding UV absorbance readings (Column 8, lines 43-46)." An ordinary practitioner would have been motivated to substitute and combine the separation of nucleic acid fragments by successively performing hydroxyapatite chromatography and HPLC of Arnold et al. into the identification and banding of human chromosome of Sicilliano et al. in view of Cronin et al., in order to achieve the express

advantages, as noted by Arnold et al., of a purification step utilizing hydroxyapatite that yields a highly purified product as indicated by the HPLC chromatogram and corresponding UV absorbance readings.

6. Claims 15-22 and 24-37 are rejected under 35 U.S.C. 103 (a) over Austin et al. (U.S. Patent 6,132,965) (October 17, 2000) in view of Cronin et al. (U.S. Patent 6,309,823 B1) (October 30, 2001) further in view of Sytkowski et al. (U.S. Patent 5,804,382) (September 8, 1998).

Austin et al in view of Cronin et al. teach the method of claims 15-18 as described above.

Austin et al in view of Cronin et al. do not teach the driver and tester population of nucleic acids are genomic nucleic acid sequences.

Sytkowski et al. teach the teach the driver and tester population of nucleic acids are genomic nucleic acid sequences (Abstract, Figure 1 and Claim 33).

Austin et al in view of Cronin et al. do not teach a method wherein the tester population of nucleic acids are from a genome, and the driver population of nucleic acids are from at least one region of the genome, or a variant thereof from the same species as the genome.

Sytkowski et al teach a method wherein the tester population of nucleic acids are from a genome, and the driver population of nucleic acids are from at least one region of the genome, or a variant thereof from the same species as the genome (Abstract, Figure 1 and Claim 33)

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the driver and tester population of genomic

nucleic acids of Sytkowski et al. into the method of analyzing driver and tester nucleic acids of Austin et al. in view of Cronin et al., since Sytkowski et al. state "Accordingly, an object of the invention is to provide a method for identifying differentially expressed genes and differences between genomic nucleic acid sequences (Column 1, lines 55-57)." Sytkowski et al further provides motivation as Sytkowski et al state, "The isolation and identification of differentially expressed genes is of great importance in the study of embryogenesis, cell growth and differentiation, and neoplastic transformation. Furthermore, the analysis of the differences between two complex genome holds promise for the discovery of infectious agents and probes useful for genetic studies (Column 1, lines 21-25)". By employing scientific reasoning, an ordinary practitioner would have been motivated to substitute and combine the genomic nucleic acid sequences of Sytkowski et al. into the method of analyzing driver and tester nucleic acids of Austin et al. in view of Cronin et al., in order to improve the method of analyzing nucleic acids and also in order to achieve the express advantages, as noted by Sytkowski et al., of a method that provides identification of differentially expressed genes and differences between genomic nucleic acid sequences and which is of great importance in the study of embryogenesis, cell growth and differentiation, and neoplastic transformation and which holds promise for the discovery of infectious agents and probes useful for genetic studies.

7. Claims 15-37 are rejected under 35 U.S.C. 103 (a) over Austin et al. (U.S. Patent 6,132,965) (October 17, 2000) in view of Cronin et al. (U.S. Patent 6,309,823 B1) (October 30,

2001) further in view of Sytkowski et al. (U.S. Patent 5,804,382) (September 8, 1998) further in view of Cole et al. (U.S. Patent 6,183,957) (February 6, 2001).

Austin et al in view of Cronin et al further in view of Sytkowski et al. teach the method of claims 15-22 and 24-37 as described above.

Austin et al in view of Cronin et al further in view of Sytkowski et al. do not teach the cloning of a region of genome into BAC.

Cole et al. teach the cloning of a region of genome into BAC (Abstract, Examples 1-6, Tables 1-3 and Claim 1).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the cloning of a region of genome into BAC of Cole et al. into the method of analyzing driver and tester nucleic acids of Austin et al in view of Cronin et al further in view of Sytkowski et al., since Cole et al. state "The BAC cloning system is based on the E.Coli F-factor, whose replication is strictly controlled and thus ensures stable maintenance of large constructs. BACs have been widely used for cloning of DNA from various eukaryotic species (Column 2, lines 7-11)." Cole et al further provides motivation as Cole et al state, "A central advantage of the BAC cloning system is that the F-plasmid is present in only one or a maximum of two copies per cell, reducing the potential for recombination between DNA fragments and, more importantly, avoiding the lethal over-expression of cloned bacterial genes. Further, the stability and fidelity of maintenance of the clones in the BAC library represent ideal characteristics for the identification of genomic differences (Column 2, lines 16-28)". By

employing scientific reasoning, an ordinary practitioner would have been motivated to substitute and combine the cloning of a region of genome into BAC of Cole et al. into the method of analyzing driver and tester nucleic acids of Austin et al in view of Cronin et al further in view of Sytkowski et al., in order to improve the method of analyzing nucleic acids and also in order to achieve the express advantages, as noted by Cole et al., of a method widely used for cloning of DNA from various eukaryotic species which provides reduction of the potential for recombination between DNA fragments and, more importantly, avoids the lethal over-expression of cloned bacterial genes and further provides the stability and fidelity of maintenance of the clones in the BAC library that represents ideal characteristics for the identification of genomic differences.

Response to Amendment

8. In response to amendment, all previous 102 rejections are hereby withdrawn. However, new 103(a) rejections have been included.

Response to Arguments

9. Applicant's arguments with respect to claims have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

Arun Chakrabarti,

Patent Examiner,

August 7, 2002